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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/054,562	01/22/2002	Ramaswamy Chandrashekar	HW-8-2	9225

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EXAMINER	
BASKAR, PADMAVATHI	
ART UNIT	**PAPER NUMBER**
1645	13

DATE MAILED: 11/13/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/054,562	CHANDRASHEKAR ET AL.	
	Examiner	Art Unit	
	Padmavathi v Baskar	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 August 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21, 23, 24, 27, 28 and 30 - 31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21, 23, 27, 28 and 30* is/are rejected.

7)☒ Claim(s) *24 and 31* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Response to Amendment

1. Applicant's amendment filed on 8/26/03 (Paper No: 12) is acknowledged. Claims 22 and 29 have been canceled. Claims 21 and 27 have been amended. Claims 21, 23, 24, 27, 28 and 30 - 31are pending in the application.

Rejections Maintained

2. The rejection of claims 21, 23, 27, 28 and 30 under 35 U.5.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention (written description rejection) is maintained as set forth in the previous office action.

The specification describes as part of the invention, an isolated protein of SEQ ID NO: 4, which is a Dirofilaria cuticlin protein. The specification teaches translation of SEQ ID NO: 1, the coding strand of nucleic acid molecule nDiCut-1A, yields an essentially full length parasitic helminth cuticlin protein of 387 amino acids, referred to herein as PDiCut-1A, the amino acid sequence of which is represented by SEQ ID NO: 4. The open reading frame spans from nucleotide 167 through nucleotide 1327 of SEQ ID NO: 1 and a termination (stop) codon spans from nucleotide 1329 through nucleotide 1331 of SEQ ID NO: 1. The coding region encoding PDiCut-1A, is represented by SEQ ID NO: 3 (the coding strand). However, the specification does not teach (1) an isolated Dirofilaria immitis protein or a composition comprising variants there of that are at least 95% identical to SEQ.ID.NO: 4 and have cuticlin activity.

The actual biological function of a protein variant comprising 95% identical to SEQ ID NO: 4 or variants to either or any of SEQ ID NO 2 and 5 is not set forth in this specification. USPQ2d 1111 makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that (he or she] invented what is claimed." (See Vas-Cath at page 1116).

Therefore, an isolated Dirofilaria immitis protein or a composition comprising an amino acid sequence of SEQ.ID.NO: 4 meets the written description provision of 35 U.S.C. 112, first paragraph for the reasons set forth below.

The specification fails to teach isolated Dirofilaria immitis protein or a composition comprising variants there of that are at least 95% identical to SEQ.ID.NO: 4 and have cuticlin activity.

It is noted that the claimed variants do not exist as an invention independent of their function in encoding a protein of SEQ.ID.NO: 4. Further, the specification lacks support for a protein, SEQ.ID.NO: 4 variants that are encoded by nucleic acid molecule SEQ ID NO1 or 3. The function of this protein remains to be characterized. The actual structure or other relevant

identifying characteristics of each protein having the claimed properties of the cuticlin protein can only be determined empirically by actually making every nucleic acid that encodes the recited variability (i.e. the instant 95% identity) and testing each to determine whether such a protein having the particularly disclosed properties of an helminth cuticlin protein comprising an amino acid sequence SEQ ID NO: 4. For example, if there is a well-established correlation between structure and function in the art, one skilled in the art will be able to reasonable predict the complete structure of the claimed invention from its function. Thus there is no written description support for proteins or compositions as claimed.

Applicants propose that the skilled artisan is to modify a known nucleic acid sequence encoding a known protein sequence and that modification would still describe applicant's invention as a protein comprising an amino acid sequence SEQ ID NO: 4 as disclosed. The protein has specific biological properties dictated by the structure of the protein and the corresponding structure of the structural gene sequence which encodes it. There must be some nexus between the structure of the protein encoded, and the function of that encoded protein. However, function cannot be predicted from the modification of the structure of the polynucleic acid sequences of SEQ.ID.NO: 1, SEQ.ID.NO 3 or amino acid sequence of SEQ.ID.NO: 4 because these proteins have not been described by the specification, nor would they be structurally related to SEQ.ID.NO: 4. Adequate written description requires more than a mere statement that it is part of the invention. See Fires v. Revel, 25 U5PQ2d 1601, 1606 (CAFC 1993) and Amgen Inc V Chugai Pharmaceutical Co Ltd., 18 U5PQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 U5PQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. Applicants have not described proteins that are at least 95% identical to SEQ.ID.NO: 4 and have cuticlin activity.

Applicant's arguments filed on 8/26/03 have been fully considered but they are not found persuasive.

Applicant states that they have attempted to follow the guidance set forth in Example 14 of the Synopsis Application of Written Description Guidelines, which was prepared by USPTO to train examiners how to apply the requirement set out in Federal Register, Vol 66, No: 4, pages 1099-1111 and accordingly the claims have been amended to recite "an isolated Dirofilaria immitis protein or a composition comprising variants there of that are at least 95% identical to SEQ.ID.NO: 4 and have cuticlin activity". Further, applicant explains and compares the claimed invention with Example 14 and claims that by amending the claims to recite cuticlin activity for variants.

The examiner is aware of the Written Description Guidelines and appreciate applicant's attempt to follow the guidelines prepared by USPTO to train examiners how to apply the

requirement set out in Federal Register, Vol 66, No: 4, pages 1099-1111. However, the examiner would like to bring applicant's attention to the same example 14, which clearly indicates, " the specification exemplifies a protein isolated from liver that catalyzes the reaction A →B but does not exemplify variants of the protein as the genus protein function has been exemplified. However, in the present claimed invention, the function of the protein, SEQ.ID.NO: 4 is not exemplified as required and the art does not teach such protein. The examiner has reviewed the specification and found no written description support for the claimed language. The specification on page 57 recites that cuticlin inhibitor is identified by its ability to bind to, or otherwise interact with, a parasite helminth cuticlin protein, thereby inhibiting cuticlin activity of that protein. However, neither SEQ.ID.NO: 4 nor variants have been shown to have "cuticlin activity." Thus, the claims fail to satisfy the written description requirements. Therefore, the rejection is maintained.

3. The rejection of claims 21, 23, 27, 28 and 30 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling an isolated Dirofilaria immitis protein or a composition having the amino acid sequence SEQ.ID.NO: 4, does not reasonably provide enablement for an isolated Dirofilaria immitis protein or a composition having an amino acid sequence SEQ.ID.NO: 4 and variants thereof that are at least 95% identical to SEQ.ID.NO: 4 is maintained as set forth in the previous office action.

The specification teaches nucleic acid encoding a D.immitis protein of SEQ ID N0: 4. The specification is not enabled for the claimed protein or composition comprising variants of SEQ.ID.NO: 4 because: 1) the specification fails to teach where variation of SEQ ID N0: 4 is permitted such that the protein is still able to function as a composition for inhibiting or curing or diagnosing parasitic infections; 2) the specification lacks any written description of any variant of D.immitis or Dirofilaria nematode species of SEQ ID N0: 4 which are capable of similarly function; 3) the specification fails to teach how to use protein sequences which are variant of SEQ ID N0:4 in diagnosis/detection because the specification fails to teach what are the critical

residues that can be modified and still achieve a protein variant that will function as a vaccine and (4) the art teaches that even replacement of a single amino acid residue may lead to both structural and functional changes in biological activity and immunological recognition of a protein. As to points 1)- 4), the specification fails to provide a written description of any protein variant (95% variant) and any protein encoded by the nucleotide sequence of SEQ ID N0: 1 and 3, which function equivalently. The specification fails to teach the critical protein residues involved in any function of the protein encoded by SEQ ID N0: 4 such that the skilled artisan is provided no guidance to test, screen or make the plethora of nucleic acid sequence variants of SEQ ID N0: 2 and 5 of a claimed protein of no defined structure, even using conventional technology which allow for a screening process. It is known for nucleic acids as well as proteins, for example, that even a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many instances, albeit not in all cases. The effects of these changes are largely unpredictable as to which ones have a significant effect versus not. Therefore, the citation of sequence identity or hybridization results in an unpredictable and therefore unreliable correspondence between the claimed biomolecule and the indicated similar biomolecule of known function and therefore lacks support regarding enablement. Several publications document this unpredictability of the relationship between sequence and function, albeit that certain specific sequences may be found to be conserved over biomolecule of related function upon a significant amount of further research. One of skill in the art would be reduced to merely randomly altering nucleic acids which would lead to unpredictable results regarding the functional activity of the protein or its relationship to SEQ.ID.NO: 4. Moreover, protein chemistry is probably one of the most unpredictable areas of biotechnology and the art teaches that the significance of any particular amino acid and sequences for different aspects of biological activity can not be predicted a priori and must be determined empirically on a case by case basis (Rudinger et al, in "PEPTIDE HORMONES", edited by Parsons, J.A., University Park Press, June 1976, page 6). The art specifically teaches that even a single amino acid change in a protein leads to unpredictable changes in the biological activity of the protein. For example, replacement of a single lysine residue at position 118 of the acidic fibroblast growth factor by glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (Burgess et al., The Journal of Cell Biology, 111:2129-2138, 1990). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine, or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biologic activity of the mitogen (Lazar et al., Molecular and Cellular Biology, 8(3): 1247-1252, 1988). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of a protein. Proteins with replacement of single amino acid residues may lead to both structural and functional changes in biological activity and immunological recognition. For example, Jobling et al. (Mol. Microbiol. 1991, 5(7): 1755-67 teaches a panel of single amino acid substitutions by oligonucleotide directed mutagenesis which products proteins that differ in native conformation, immunological recognition, binding and toxicity, thus exemplifying the importance of structural components to both biological function and immunological recognition. The specification has not taught which residues of the amino acid sequence of SEQ ID N0: 4 can be varied and still achieve a protein that is functional as claimed. Further, random insertions, deletions and changes to a nucleotide sequence do not provide guidance to make a related protein. Therefore, the claimed isolated protein results in an unpredictable biomolecule without any function. Therefore, lacks support regarding the scope of enablement.

Applicant's arguments filed on 8/26/03 have been fully considered but they are not found persuasive.

Applicant claims that the examiner's rejection appears to focus on the issue of protein variants and whether or not sufficient guidance is provided to teach one skill in the art which residues may be modified and still retain protein function. Further applicant states that the examiner's position is not supported by case law and cites case laws.

The examiner made it clear on the record that the invention as claimed does not meet the written description guidelines and evaluated the claims for scope of enablement based on the Wands analysis. MPEP: 2164.08

The nature of the disclosed invention is an isolated protein SEQ ID NO: 4 from D.immitis. However, the activity of this protein is not known in the art, not characterized by the present invention and the art is underdeveloped to predict the function of this protein. Therefore, one skilled in the art is forced to perform undue experimentation to make and use the invention commensurate in scope with these claims, The Federal Circuit has repeatedly held that "the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. Moreover, protein chemistry is probably one of the most unpredictable areas of biotechnology and the art teaches that the significance of any particular amino acid and sequences for different aspects of biological activity can not be predicted a priori and must be determined empirically on a case by case basis. Finally, applicant on one hand believes the function of the protein is important to satisfy the written description guidelines under 35 U.S.C. 112 first paragraph and on the other hand states that functionality is not required to satisfy the first paragraph (*In re Fisher*). These arguments are not consistent. The breadth of a claim relevant to enablement, the only relevant concern should be whether the

scope of enablement provided to one skilled in the art by the disclosure. However, no such disclosure is present in the specification. Therefore, this rejection is maintained,

4. Claims 24 and 31are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Status of claims

5. Claims 24 and 31are objected

Claims 21, 23, 27, 28 and 30 are rejected.

Conclusion

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Padma Baskar whose telephone number is (703) 308-8886. The examiner can normally be reached on Monday through Friday from 6:30 AM to 4 PM EST

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

Padma Baskar Ph.D.

11/10/03

MARK NAVARRO
PRIMARY EXAMINER